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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,358	03/26/2004	Ker-Sang Chen	9188R&	1244

27752 7590 08/23/2006

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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/810,358	CHEN ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *7,8,13,14 and 24-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-12 and 16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/20/04,10/29/04*. 6/30/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' election with traverse of Group I, claims 1-23, drawn to a method and kits for determining efficacy of a treatment of inflammatory diseases of the bowel *in vivo* in the reply filed on 15 June 2006 in response to the 16 May 2006 office action is acknowledged. In response to Election of Species requirement, applicants elect interleukin-10 as the anti-inflammatory cytokine, interleukin-12 as the pro-inflammatory cytokine and a probiotic as the compound inducing *in vitro* stimulation. The traversal is on the ground(s) that the methods of Group I and II are directed to the same goal. Applicants' arguments have been fully considered but are not found to be persuasive for the following reasons: the methods of Group I are directed to methods involving *in vivo* determinations, while the methods of Group II are directed to an *in vitro* screening method. The methods of Invention I requires search for a specific patient population, which is not required for the methods of Invention II. The search for the two methods would not be coextensive and would provide a serious search burden on the Examiner and the resources of the USPTO.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 9-12, 16-23 are under consideration to the extent they read on the elected invention. Claims 7, 8, 13, 14, and 24-45 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

It is noted that Claim 22 appears to be written so as to invoke 112, 6th paragraph which states:

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in

support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Claims 22 and 23 will be evaluated under 35 U.S.C. 112, sixth paragraph.

Objections

Information Disclosure:

References submitted on IDS filed 20 June 2004 are not in compliance with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 for the following reasons: Reference 1 on page 2 of 5 does not indicate the author or year; reference 2 on page 2 of 5 does not indicate the appropriate author; references 3, 4, 8, 12 and 13 on page 2 of 5 do not indicate the year or source. References 1 and 10 on page 3 of 5 do not indicate the year or source; reference 13 on page 3 of 5 does not indicate the year of the reference. Reference 1 on page 4 of 5 does not indicate the source; reference 10 does not indicate the year. Reference 1 on page 5 of 5 is duplicative of Reference 14 on page 3 of 5. Therefore, these references have been lined through and have not been considered.

References submitted on IDS filed 30 June 2005 are not in compliance with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 for the following reasons: Reference 1 does not identify applicant of cited document; reference 2 does not identify applicant or publication date of cited document. Therefore, these references have been lined through and have not been considered.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claims:

Claims 2-5 and 12 are objected to as encompassing non-elected inventions. Appropriate correction is required.

Claim Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is an incomplete method claim. To be complete, a method claim must state a goal in the preamble of the claim, and conclude having achieved that goal. The preamble of the claim recites "a method of determining the efficacy of a treatment...". The conclusionary statement recites "wherein an increase in the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine.....is indicative of an inhibitor of inflammatory diseases of the bowel, and no change or decrease in the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine.....is indicative said treatment not being an inhibitor of inflammatory diseases of the bowel." Thus, the goal set forth in the preamble, is not identical to one stated at the conclusion, so it is unclear what the claim is directed to. Additionally, it is unclear if applicants intend to inhibit recurrence of disease, inhibit progression of disease or inhibit pathogenesis.

Claims 2 and 3 recite improper Markush groups. A proper Markush Group recites members as being "selected from the group consisting of A, B and C" (See MPEP 2173.05(h)).

Additionally, Claims 1, 6 and 22 recite the terms "anti-inflammatory cytokine" and "pro-inflammatory cytokine". Claims 2, 3, and 16-18 recite "anti-inflammatory cytokine"; claims 4, 5, and 19-21 recite "pro-inflammatory cytokine". These terms render the claims vague and indefinite. The art recognizes that individual cytokines have multiple target cells and multiple actions. Cytokine action is contextual. Therefore, whether a cytokine is anti-inflammatory or pro-inflammatory is influenced by the milieu in which they act and the presence or absence of other biologically active agents.

Claims 2-5 are vague and indefinite for reciting specific cytokines and "mixtures thereof". It is unclear if applicants intend to measure one, two or more cytokines individually, or all together and which cytokines applicants intend to mix and measure. It is also unclear if applicant intends all of the recited elements to be used together or separately.

Claim 6 is vague and indefinite in the recitation of "wherein said ration of anit-inflammatory cytokine to pro-inflammatory cytokine is interleukin-10/interleukin-12". A ratio is commonly defined as a quotient of two mathematical expressions. It is suggested that claims be amended to recite wherein said anti-inflammatory cytokine is interleukin-10 and said pro-inflammatory cytokine is interleukin 12.

Claims 9-11 are vague and indefinite for reciting "peripheral blood mononuclear cells with *in vitro* stimulation". It is not clear if the stimulation is to occur prior to or during or after sample collection. Additionally, the claims recite specific biological samples and "mixtures thereof". It is unclear if applicants intend to measure cytokine levels in each biological sample and combine the results or measure cytokine levels in a mixture of two or more biological samples. It is also unclear if applicant intends all of the recited elements to be used together or separately.

Claim 12 is vague and indefinite for reciting "wherein said *in vitro* stimulation comprises a mitogen, probiotic, anti-CD3 molecule and mixtures thereof." A mitogen, probiotic and anti-CD3 molecule is a means of providing stimulation, and cannot

comprise stimulation. Furthermore, it is unclear what applicants intend the recited mixtures to comprise. It is also unclear if applicant intends all of the recited elements to be used together or separately.

Claim(s) 16-21 recites the limitation "the method according to claim....wherein the means for measuring the levels of ....cytokines". There is insufficient antecedent basis for this limitation in the claim.

Claims 16, 17, 19, and 20 are vague and indefinite for reciting numerous assay methodologies and "mixtures thereof". It is unclear how applicant intends to utilize a mixture of methods to measure cytokine levels. It is also unclear if applicant intends all of the recited elements to be used together or separately. Additionally, claims 16 and 19, which recite means of measuring cytokines, include methods such as RT-PCR, competitive reverse transcription PCR, Northern blots, gene arrays and direct measurement of m-RNA. These methods measure nucleic acids, not proteins, and therefore would be unable to measure cytokine levels.

It is noted that Claim 22 appears to be written so as to invoke 112, sixth paragraph. However, the phrase "means for" is not recited the claims. If applicants intend to invoke 112, sixth paragraph, then the claims must be amended to recite "means for".

Claim 22 is vague and indefinite for reciting a "measuring element or system". An element or system does not recite any structural limitations. It is unclear how an element or system could be utilized to measure levels of a protein, such as a cytokine.

Claims 18 and 23 are included in the rejection as being dependent upon rejected claims.

35 U.S.C. § 112, First Paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim(s) 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo* comprising the steps of

a. measuring the level of at least one anti-inflammatory cytokine wherein the anti-inflammatory cytokine is **IL-10** and at least one pro-inflammatory cytokine wherein the pro-inflammatory cytokine is **IL-12**, **TNF-α** or **IFN-γ** in a biological sample from a mammalian subject wherein the biological sample comprises **peripheral blood mononuclear cells with *in vitro* stimulation**

b. determining the ratio of at least one anti-inflammatory cytokine wherein the anti-inflammatory cytokine is **IL-10** and at least one pro-inflammatory cytokine wherein the pro-inflammatory cytokine is **IL-12**, **TNF-α** or **IFN-γ**

c. administering said treatment wherein said treatment comprises administration of **probiotic material**

d. measuring the level of at least one anti-inflammatory cytokine wherein the anti-inflammatory cytokine is **IL-10** and at least one pro-inflammatory cytokine wherein the pro-inflammatory cytokine is **IL-12**, **TNF-α** or **IFN-γ** in a biological sample from a mammalian subject wherein the biological sample comprises **peripheral blood**

mononuclear cells with *in vitro* stimulation at a time following administration of said treatment

e. determining the ratio of at least one anti-inflammatory cytokine wherein the anti-inflammatory cytokine is **IL-10** and at least one pro-inflammatory cytokine wherein the pro-inflammatory cytokine is **IL-12**, **TNF-α** or **IFN-γ** following administration of said treatment

wherein an increase in the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine following the administration of said treatment is indicative of an **efficacy** of treatment of inflammatory diseases of the bowel and no change or decrease in the ration of anti- inflammatory cytokine to pro-inflammatory cytokine following the administration of said treatment is indicative said treatment is **not effective** in treatment of inflammatory disease of the bowel

does not reasonably provide enablement for a method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo* comprising the steps of:

a. measuring the level of at least one of **any** anti-inflammatory cytokine and at least one of **any** pro-inflammatory cytokine in **any** biological sample from a mammalian subject;

b. determining the ratio of the at least one of **any** anti-inflammatory cytokine to the at least one of **any** pro-inflammatory cytokine;

c. administering **any** (unspecified) treatment;

d. measuring the level of at least one of **any** anti-inflammatory cytokine and at least one of **any** pro-inflammatory cytokine in **any** biological sample from a mammalian subject at a time following administration of said treatment;

e. determining the ratio of the at least one of **any** anti-inflammatory cytokine to the at least one of **any** pro-inflammatory cytokine following administration of said treatment;

wherein an increase in the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine following administration of said treatment is indicative of an **inhibitor** of

inflammatory diseases of the bowel and no change or decrease in the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine following the administration of said treatment is indicative said treatment is **not an inhibitor** of inflammatory disease of the bowel.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Claim 1 is broadly drawn to a method of determining **efficacy** of **any** treatment of inflammatory diseases of the bowel *in vivo* in mammals comprising the steps of:

a. measuring the level of at least one of **any** anti-inflammatory cytokine and at least one of **any** pro-inflammatory cytokine in **any** biological sample from a mammalian subject;

b. determining the ratio of the at least one of **any** anti-inflammatory cytokine to the at least one of **any** pro-inflammatory cytokine;

c. administering **any** (unspecified) treatment;

d. measuring the level of at least one of **any** anti-inflammatory cytokine and at least one of **any** pro-inflammatory cytokine in **any** biological sample from a mammalian subject at a time following administration of said treatment;

e. determining the ratio of the at least one of **any** anti-inflammatory cytokine to the at least one of **any** pro-inflammatory cytokine following administration of said treatment;

wherein an increase in the ration of anti-inflammatory cytokine to pro-inflammatory cytokine following administration of said treatment is indicative of an **inhibitor** of inflammatory diseases of the bowel.

These broad claims are not enabled for the broad scope for the following reasons. The specification teaches that the method of the instant invention, as outlined above may be "utilized to both screen and clinically evaluate unknown or new treatments for efficacy in the treatment of inflammatory disease of the bowel....the method of the present invention may also be used to monitor the efficacy of a known treatment in an individual patient with inflammatory disease of the bowel.....the method herein may be used to provide a predictive biomarker for inflammatory disease of the bowel helpful in diagnosis of the disorder" (page 6, lines 10-16). "The treatment herein include any treatment and/or compositions for use in the treatment of inflammatory diseases of the bowel.....include[ing] anti-inflammatory drugs, probiotic compositions, new compositions and new compounds not known to have efficacy in the treatment of inflammatory diseases of the bowel, compositions and compounds not known to have efficacy in the treatment of inflammatory disease of the bowel....." (page 7, lines 3-11). However, the specification and working examples all disclose only one method of treatment of inflammatory bowel disease, daily feeding of probiotic preparation containing *Bifidobacterium infantis* (page 14, lines 6-8). The etiologies of inflammatory bowel diseases are complex and remain poorly understood, with several genetic and environmental factors implicated in the pathogenesis of IBD (2000. Papadakis et al. Ann. Rev Med. 51: 289-298, page 289, 1st paragraph). These diseases are controlled by a wide variety of treatments including dietary regimens, and drugs including aminosalicylates, antibiotics, antimetabolites, corticosteroids, antirheumatic drugs and immunomodulators. Some treatment modalities involve administration of cytokines and anti-cytokines, including anti-TNF-α and IL-10 (Papadikis et al, page 295, 4th

paragraph). One would predict that administration of such compounds would alter the ratio of anti-inflammatory to pro-inflammatory cytokines in biological samples, but these alterations would be due to administration of the drugs, and would not indicate efficacy of treatment. Thus, one of ordinary skill in the art would be unable to predict whether one could evaluate the efficacy of **any** (unspecified) treatment by measuring changes in the ratio of anti-inflammatory to pro-inflammatory cytokines.

Furthermore, the specification teaches that the "methods of the present invention comprise the step of measuring at least one anti-inflammatory and at least one pro-inflammatory cytokine levels in a biological sample obtained from a mammalian subject (page 11, lines 4-6). The art recognizes, and the specification teaches, "cytokines are pleitropic and express multiple biologically overlapping activities" (page 11, lines 7-8). Rogler et al (1998. World J Surg. 22:382-389, cited on IDS of 20 July 2004, page 4 of 5, reference 8) teach that cytokines play a central role in modulation of the intestinal immune system and lists numerous cytokines having pro- and anti-inflammatory functions (abstract). However, the working examples recite only one anti-inflammatory cytokine, IL-10, and three pro-inflammatory cytokines, is IL-12, TNF-α or IFN-γ. One of ordinary skill in the art would have to undertake undue experimentation to determine which cytokines have anti- or pro-inflammatory actions within the context of the system disclosed by the instant invention, and then determine whether changes in the ratio of anti-inflammatory to pro-inflammatory cytokines would be indicative of efficacy of treatment.

The specification teaches "the method of the present invention comprises measuring cytokine levels in biological sample obtained from a mammalian subject both before and during or after administration of said treatment..."biological sample" includes urine plasma, serum, saliva, tissue biopsies, cerebrospinal fluid, peripheral blood mononuclear cells (PBMC) with *in vitro* stimulation, peripheral blood mononuclear cells without *in vitro* stimulation, gut lymphoid tissues with *in vitro* stimulation, gut lymphoid tissues without *in vitro* stimulation, gut lavage fluids and mixtures thereof. The specification discloses one method of determining the efficacy of treatment. Patients are treated with probiotic mixtures, blood is drawn, and changes in the ratio of pro to

anti-inflammatory cytokines are measured in culture media of PBMC following stimulation of PBMC with LPS, or several types of bacteria. Thus, the only working example of the instant invention is a combination of an *in vivo* treatment method and an *in vitro* method of evaluating the efficacy of treatment. Rogler et al. teach that numerous cytokines may be involved in the mucosal immune system; these are synthesized and secreted by many different cells of the immune system (page 382, 2nd column, 1st paragraph). Thus, cytokine levels in samples such as serum, saliva or urine reflect cytokine levels from multiple sources. One would not be able to predict that changes in the ratios of levels anti-inflammatory to pro-inflammatory cytokines in such biological samples as serum or urine, reflecting the cytokines synthesized and secreted by multiple sources, would be indicative of effectiveness of treatment for IBD.

The conclusionary portion of claim 1 recites that "an increase in the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine following the administration of said treatment is indicative of an inhibitor of inflammatory diseases of the bowel....". However, the specification does not teach a nexus between changes in the ratio of anti-inflammatory cytokine to pro-inflammatory cytokine and any objective indication of an inhibition of any inflammatory bowel disease; the specification discloses a correlation between the change in cytokine ratios and a change in abdominal pain (page 25, Table 1). One of ordinary skill in the art would recognize that perceived relief of specific symptoms of a given disease would not necessarily be indicative of an inhibition of actual disease progression. Thus, one would not be able to predict that a change in the ratios of levels anti-inflammatory to pro-inflammatory cytokines would be correlative of any objective indications of inhibition of inflammatory bowel disease.

Due to the large quantity of experimentation necessary to determine which potential treatments would result in alteration of the ratio of pro- and anti-inflammatory cytokines in a biological sample, the identification of which cytokines measured in the methods of the instant invention would indicate efficacy of treatment, and which biological samples should be utilized in measurement of same, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples other than the one indicated above, the complex nature of the

invention, the state of the prior art which establishes that whether a cytokine is anti-inflammatory or pro-inflammatory is influenced by the milieu in which they act and the presence or absence of other biologically active agents and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim(s) 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a kit comprising

a. components for measuring the level of at least one anti-inflammatory cytokine in a biological sample, wherein the anti-inflammatory cytokine is **IL-10** and wherein the biological sample from a mammalian subject comprises **peripheral blood mononuclear cells with *in vitro* stimulation,** before treatment and at least one time point after or during treatment

b. a component for measuring at least one pro-inflammatory cytokine in a biological sample, wherein the pro-inflammatory cytokine is **IL-12**, **TNF-α** or **IFN-γ** and wherein the biological sample from a mammalian subject comprises **peripheral blood mononuclear cells with *in vitro* stimulation,** before treatment and at least one time point after or during treatment

wherein the increase in ratio of **IL-10** to **IL-12**, **TNF-α** or **IFN-γ** is indicative of **efficacy** of treatment for inflammatory disease of the bowel.

does not reasonably provide enablement for a kit comprising

a. components for measuring the level of at least one of **any** anti-inflammatory cytokine in **any** biological sample, before treatment and at least one time point after or during treatment

b. components for measuring at least one of **any** pro-inflammatory cytokine in **any** biological sample, before treatment and at least one time point after or during treatment

wherein the increase in ratio of **IL-10** to **IL-12**, **TNF-α** or **IFN-γ** is indicative of **an inhibitor** for inflammatory disease of the bowel.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification discloses that kits are provided for carrying out the method of the present invention (page 13, lines 12-13). As discussed above, the specification envisions measurement of **any** anti- or pro-inflammatory cytokine in **any** biological sample wherein an increase in the ratio of anti- to pro-inflammatory cytokine following treatment is indicative an inhibitor of inflammatory diseases of the bowel. However, the working examples disclose only the measurement of changes in the ratio of **IL-10** to **IL-12**, **TNF-α** or **IFN-γ** after treatment in a system comprising *in vitro* stimulation of **peripheral blood mononuclear cells.** Table 1 teaches a correlation between the change in cytokine ratios and a change in abdominal pain. Therefore, the kit could be utilized only in determining the efficacy of treatment in relieving symptoms of inflammatory bowel disease, but not in determining inhibition of inflammatory bowel disease.

Due to the large quantity of experimentation necessary to determine which cytokines measured by the kits of the instant invention would indicate efficacy of treatment, and which biological samples should be utilized in measurement of same, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples other than the one indicated above, the complex nature of the invention, the state of the prior art which establishes that whether a cytokine is anti-inflammatory or pro-inflammatory is influenced by the milieu in which they act and the presence or absence of other biologically active agents and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Vignali (2000 Journal of Immunological Methods 243:243-255).

Claim 22, given its broadest reasonable interpretation, is drawn to a kit for measuring cytokines in a biological sample from a mammalian subject. There are no structural limitations recited as to the contents of said kit.

Vignali teaches a FlowMetrix System of quantifying the concentration of 15 cytokines simultaneously in a 100 µl sample (page 248, 2nd column, section 60). The reference teaches the uses of the assay methodology to measure cytokine levels in an animal model for toxic shock syndrome. Therefore, the teachings of Vignali anticipate all the limitations of claim 22.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vignali (2000 Journal of Immunological Methods 243:243-255). Vignali teaches a kit for measuring cytokines in a biological sample from a mammalian subject. Vignali does not teach a kit further comprising means for obtaining said biological samples. It would have been obvious to include a device for obtaining said biological samples in the kit taught by Vignali. The person of ordinary skill in the art would have been motivated to make that modification because Vignali teaches use of the assay system to measure cytokine levels in animal models and it would increase efficiency to include sampling devices along with the materials necessary to measure the cytokines. One would reasonably have expected success because kits by various manufacturers contain a wide variety of materials.

Conclusions:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS